Journal of Surgical Oncology 63:179–182 (1996)

Pattern of Second Primary Neoplasms Following Breast Cancer

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Background: Second primary neoplasms (SPN) have been seen with diseases such as breast cancer and Hodgkin's disease. Therapeutic agents used for their treatment have been found responsible for the development of SPN in some cases. In addition, genetic factors are known to contribute to their development.
Methods: A retrospective study of 15 patients who had primary breast cancer and developed SPN concurrently or sequentially was conducted.
Results: Of 15 patients analysed in this study, five had haematological SPN, four had ovarian cancer, and six had different types of non-haematological SPN. Familial clustering was found in two patients. A peculiar abnormality of chromosome 5 and 7 was detected in one patient with haematological SPN, suggesting therapy-related leukeamia.
Conclusions: It is postulated that alkylating agents with or without p53 gene inactivation may predispose to leukaemia, whereas ovarian tumours following breast cancer could be related to BRCA 1 gene inactivation.

KEY WORDS: **leukaemia, ovarian cancer, p53 gene, BRCA 1 gene, alkylating agent**

INTRODUCTION

Improved survival of cancer patients with multimodality treatment is leading to an increased incidence of second primary neoplasms (SPN). This is especially true for breast cancer and Hodgkin's disease. Development of SPN has been related to therapy, genetic predisposition, or environmental agents including viral agents [1]. The present study shows the pattern of SPN following breast cancer and discusses the interaction of various predisposing factors.

MATERIALS AND METHODS

Fifteen cases with SPN following breast cancer have been documented at Tata Memorial Hospital since 1982. All these patients have been evaluated retrospectively regarding various clinical characteristics, and complete details of their primary diagnosis and treatment, including type of surgery, cumulative doses of all chemotherapeutic agents, and total dose of radiation. The clinical characteristics, histology, and management of various SPN were also documented. Cytogenetic data were available in only one patient who had haematological SPN.

RESULTS

Table I shows various clinical characteristics of the 15 patients. All were female patients with median age of 50 years (range 30–60 years). Surgery was carried out for all primary breast cancer patients. Thirteen patients underwent modified radical mastectomy, and sector mastectomy and simple mastectomy were done in one patient each.

Five patients received CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy following surgical management. Of these, one patient also received ifosfamide, velbe, and mitomycin. Two patients received hormonal therapy in the form of tamoxifen. The median cumulative dose of cyclophosphamide given was 3 gm (range 3–10.8 gm). Six patients received radiotherapy at a median dose of 5,000 rads (range 4,000–6,500 rads) to

Accepted for publication August 25, 1996.
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TABLE I. Characteristics of Primary Breast Neoplasms

Case no.	Age (yrs)	Surgery[a]	Chemotherapy cumulative doses (g)			Radiotherapy (yes/no)
			C[b]	M[c]	F[d]	
1.	58	MRM	10.8	1	10.8	Yes
2.[e]	60	MRM	–	–	–	No
3.	50	SM	–	–	–	No
4.	35	MRM	–	–	–	No
5.	55	MRM	6	0.3	6	Yes
6.	54	MRM	3	0.15	3	Yes
7.	50	MRM	–	–	–	Yes
8.[f]	42	MRM	3	0.3	3	Yes
9.	39	MRM	–	–	–	No
10.	50	M	–	–	–	Yes
11.	30	MRM	–	–	–	No
12.	58	MRM	–	–	–	No
13.	40	MRM	3	0.09	3	No
14.[e]	50	MRM	–	–	–	No
15.	47	MRM	–	—	–	No

[a]MRM = modified radical mastectomy, SM = sector mastectomy, M = simple mastectomy.
[b]Cyclophosphamide.
[c]Methotrexate.
[d]Fluorouracil.
[e]Patient received tamoxifen only.
[f]This patient received ifosfamide, mitomycin and velbe in addition to CMF.

the local chest wall area. Four patients received combined modality treatment with chemotherapy and radiotherapy.

During follow-up of breast cancer patients, 15 patients with SPN have been documented. There were 5 haematological and 10 nonhaematological malignancies. Table II shows details of nonhaematological SPN. Among these 10 nonhaematological malignancies, there were four cases of ovarian cancer and one case each of cancer of the cervix, cancer of the rectum, cancer of the tongue, cancer of the bronchus, fibrous histiocytoma, and non-Hodgkin's lymphoma of the nasopharynx. The median duration from primary diagnosis to SPN was 3 years (range 0–16 years). In one patient (case no. 4), breast cancer and cancer of the rectum were found concurrently.

Table III shows details of five patients with haematological SPN. This group had two cases of acute myeloid leukaemia and one case each of myelodysplastic syndrome, chronic lymphocytic leukaemia, and acute promyelocytic leukaemia. The bone marrow from one patient with acute myeloid leukaemia revealed cytogenetic abnormality of chromosome 5 and 7.

Among the nonhaematological malignancies, four patients with ovarian carcinoma underwent debulking surgery followed by chemotherapy with cisplatin and cyclophosphamide. The patient with cervical cancer received local radiotherapy. The patient with nasopharyngeal non-Hodgkin's lymphoma was treated with aggressive chemotherapy followed by radiotherapy. All these patients showed good clinical response.

All patients with haematological malignancies were given supportive care only.

Family history was significant in two patients. One patient (case no. 9) had a sister with breast cancer and mother with an ovarian tumour. Another patient (case no. 11) had a grandmother with breast cancer, mother with lung cancer, and sister with ovarian cancer. In the remaining 12 patients, the family history was noncontributory.

DISCUSSION

Breast cancer is known to be associated with various SPNs such as leukaemia, multiple myeloma, gynaecological malignancies, Hodgkin's disease, lung cancer, gastrointestinal cancer, and dermatological cancer. [1,2]. Of these, leukaemia and gynaecological malignancies predominate. The present study also showed a similar picture with five gynaecological and five haematological malignancies as SPN following breast cancer.

Since breast cancer is treated with multimodality treatment, chemotheraputic agents, especially such alkylating agents as cyclophosphamide and radiotherapy were thought to be responsible for developing SPN.

Therapy-related SPN are frequently haematological malignancies. *Therapy-related acute nonlymphocytic leukaemia (ANLL)* is a well-established entity [1]. Fisher et al. [3] have shown a leukaemia risk of 1.29% at 10 years in women who received adjuvant chemotherapy for breast cancer. The risk is of minor importance compared to the relative benefit of adjuvant chemotherapy. Therapy-related ANLL is preceded by preleukaemic phase of myelodysplastic changes, and it is accompanied by typical cytogenetic abnormalities of chromosome 5 and 7, namely, absence of chromosome 5 or 7, i.e., -5 or -7, absence of the long arm of chromosome 5, i.e., 5q-[4–6].

TABLE II. Characteristics of Non-Haematological Second Primary Neoplasms Following Breast Cancer

Case no.	Type	Duration from primary neoplasm	Management and response[a]
2	NHL[c]—nasopharynx	6 years	MACOP-B + RT (CR)
3	CA[c] cervix	2 years	RT + surgery (CR)
4	CA[c] rectum	Concurrent	–
5	CA[c] tongue	2 years	–
9	fibrous histiocytoma	5 years	–
10	CA[c] ovary	3 months	Surgery + C P (PR)
11	CA[c] ovary	6 years	Surgery + C P (CR)
12	CA[c] ovary	15 years	C P
14	CA[c] bronchus	5 years	Local RT
15	CA[c] ovary	3 years	Surgery + C P (on therapy)

[a]MACOP-B = aggressive protocol consisting of methotrexate, adriamycin, cyclophosphamide, vincristine, predniosolone, bleomycin; RT = radiotherapy; CR = complete response; C = cyclophosphamide; P = cisplatin; PR = partial response.
[b]Non-Hodgkin's lymphoma.
[c]Carcinoma.

TABLE III. Characteristics of Haematological Second Primary Neoplasms Following Breast Cancer

Case no.	Types[a]	Duration from primary neoplasm	Cytogenetics[b]
1	AML M_3	2 years	–
6	AML M_2	8 years	–
7	AML	11 years	Abn chr. 5 & 7
8	MDS	5 years	–
13	CLL	16 years	–

[a]AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome; CLL = chronic lymphocytic leukaemia.
[b]Abn = abnormal; Chr = chromosomes.

In the present study, there were three cases of ANLL and one case each of myelodysplastic syndrome and chronic lymphocytic leukaemia. Four out of five patients with haematological SPN did receive adjuvant chemotherapy, including alkylating agent for primary breast cancer. Cytogenetic abnormality involving chromosome 5 and 7 was found in one patient with ANLL. In the literature, most of the therapy-related ANLL are of M_1, M_2, or M_4 (FAB) subtypes. We came across one patient with therapy-related ANLL of M_3 subtype.

Rosner et al. [1] reported leukaemia and breast cancer either sequentially or concurrently. They proposed a common aetiological factor for this co-existence of leukaemia and breast cancer. Conversely, Valagussa et al. [2] reported that there was no evidence of increased risk of SPN in breast cancer patients treated with chemotherapy compared to those who did not recieve chemotherapy.

Family history always has been important in breast cancer patients [7]. Breast cancer is detected with increased incidence in patients with a history of breast cancer in their sister and/or mother. Clustering of various other malignancies, such as soft tissue sarcoma, brain tumours, leukaemia, osteosarcoma, adrenal carcinoma, and lung carcinoma, is seen along with breast cancer as a part of the *Li-Fraumeni syndrome* [8]. The *p53 gene* is known to play a pivotal role in the Li-Fraumeni syndrome [9]. The p53 functions as a negative regulator of cell growth and also inhibits transformation of cells. Cells with p53 mutations show more genomic instability and have less ability to repair DNA damage, differentiate, or undergo apoptosis. In two of our patients, strong family histories indicate genetic predisposition.

Gallion et al. [10] have mentioned *breast ovarian cancer syndrome*, which has an autosomal dominant inheritance. In such families, gene carriers have at least an 80% lifetime chance of getting breast and/or ovarian cancer. This is related to the *BRCA 1 gene* situated on the long arm of chromosome 17. It is a tumour suppressor gene. Hence, allele losses of this gene leads to familial occurrence of breast and ovarian cancers. Four of our patients had both breast and ovarian cancers.

From the pattern of SPN in our study, it appears that there are multiple predisposing factors for the development of SPN. Also, the nature of SPN is determined by a predominant predisposing factor. Our data support the hypothesis that BRCA 1 gene inactivation predisposes to breast cancer followed by ovarian malignancy, whereas alkylating agents in association with p53 gene rearrangement predispose to haematological and other infrequent malignancies.

Genetic studies done at the time of primary diagnosis of breast cancer can help us predict the probability of SPN, or the probability of developing malignancy in other close relatives of the patients.

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